Research Paper

Efficacy of Sertraline Combined with Agomelatine in the Treatment of Depression and its Influence on Cognitive Function

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This study investigates the efficacy of sertraline combined with agomelatine in the treatment of mild to moderate depression and its impact on cognitive function. A retrospective analysis was made considering 90 individuals with mild to moderate depression. According to the actual medication, they were divided into research group and control group, with 45 individuals in each group. Both the groups were given sertraline, and the research group was given a combination of agomelatine along with sertraline for 6 w. The clinical effects, positive and negative symptom scores, depression scores, sleep quality index scores, cognitive function scores and adverse drug events were compared between the two groups. After medication, the clinical effect of the research group was better than that of the control group ($p<0.05$). The depression score, positive and negative symptom scores, and sleep quality index scores of the research group were lower than those of the control group ($p<0.05$). The cognitive function score of the research group was higher compared with the control group ($p<0.05$). There was no significant difference in adverse drug events between the two groups ($p>0.05$). Compared with the use of sertraline alone, sertraline combined with agomelatine has better clinical effects in the treatment of mild to moderate depression, helping to relieve individuals' depressive symptoms, sleep quality, cognitive function, and drug safety is high.

Key words: Sertraline, agomelatine, depression, norepinephrine, neurotransmitters

Depression is a common mental illness, and its main features are low mood, loss of interest, decreased willpower, self-denial, self-blame, poor attention, concentration, poor sleep quality, and suicidal tendencies. The inducing mechanism of depression is a relatively complex issue, and there is no clear conclusion yet. Studies have found that people with a family history of depression have a higher risk of developing the disease, and genetic factors may affect the susceptibility to depression and the genetic variation of the disease[1]. Studies have also linked depression to abnormalities in brain chemicals, such as imbalances in neurotransmitters such as serotonin, dopamine, and norepinephrine[2]. Changes in brain activity and neural circuits may be associated with the onset of depression. Studies have pointed out that neuroinflammation and immune system abnormalities may be related to the pathogenesis of depression[3]. Chronic inflammation and immune activation may lead to changes in neurotransmitters and neural circuits, thereby increasing the risk of depression. Negative effects of life events may also increase the risk of depression, such as unemployment, divorce, bereavement, bankruptcy, prison, etc. It is generally believed that women and adolescents including middle-aged people are more likely to suffer from depression than men[4].

For the treatment of depression, there are mainly psychotherapy and drug treatment. Common psychotherapy methods include cognitive behavioral therapy, supportive therapy, interpersonal therapy, and analytical therapy. Generally, through communication with a psychologist, patients can understand and change negative thinking patterns, ways of solving problems, and improve self-awareness and coping skills.

Anti-depressant drugs mainly include selective serotonin reuptake inhibitors, conventional tricyclic antidepressants, norepinephrine and

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dopamine reuptake inhibitors, conventional monoamine oxidase inhibitors, melatonin receptor agonists, etc. Selective serotonin reuptake inhibitors include sertraline, fluoxetine, paroxetine, etc., which improve depressive symptoms by increasing the concentration of serotonin in the brain. Conventional tricyclic antidepressants include amitriptyline, imipramine, etc., which reduce depressive symptoms by affecting the uptake and metabolism of various neurotransmitters. Norepinephrine and dopamine reuptake inhibitors include venlafaxine, etc., which improve depressive symptoms by increasing the concentrations of norepinephrine and dopamine. Conventional monoamine oxidase inhibitors include phenelzine, imosulfuron, etc., which increase the concentration of neurotransmitters by inhibiting the activity of monoamine oxidase. Melatonin receptor agonists include agomelatine, etc., which can improve sleep and mood problems by regulating the activity of melatonin receptors and 5-Hydroxytryptamine (5-HT) receptors. Sertraline and agomelatine were selected as medications in this study, because sertraline is one of the most widely used drugs for depression, and the research on sertraline is very representative. Agomelatine is a new type of antidepressant drug, and its mechanism is different from traditional antidepressant drugs. Agomelatine is an agonist of the endogenous hormone melatonin receptor and is also a 5-HT_{2C} receptor antagonist. It is also necessary to study this new type of antidepressant drug.

MATERIALS AND METHODS

General data:

A retrospective analysis was conducted among 90 individuals with mild to moderate depression who were admitted to Wenzhou Seventh People's Hospital from January 2020 to January 2023. According to the actual medication, they were divided into a research group and a control group, each with 45 individuals. Both the groups were given sertraline, and the research group was given a combination of agomelatine with sertraline, whose course of treatment was 6 w.

The research group included 17 males and 28 females; the course of disease was (1.63±0.28) y; the average age was (45.58±4.52) y old. According to the depression symptom rating scale, there were 9 patients with mild depression and 36 patients with moderate depression. The control group had 19 males and 26 females whose course of disease was (1.62±0.28) y; the average age was (45.34±4.33) y old. 11 patients were having mild depression and 34 patients were having moderate depression. There was no significant difference in the basic data between the two groups ($p>0.05$).

Inclusion criteria:

Patients whose age was ≥16 y and who had normal communication skills; Hamilton Rating Scale for Depression (HRSD) score ≥17 points; no antidepressant or sedative drugs 1 mo before diagnosis and treatment were included in the study.

Exclusion criteria:

Pregnant or breastfeeding women; overweight patients, diabetic patients; non-alcoholic liver patients; patients with other mental illnesses; patients with cancer; patients allergic to the drug used in this study were excluded.

Medication method:

Control group: All the patients were orally given 1 sertraline hydrochloride tablet daily for 6 w (manufacturer: Pfizer Pharmaceutical Co., Ltd., Approved by the State Drug Administration-H10980141, specification 14 tablets×50 mg) and the dose was adjusted the dose according to the patient condition after 1 w. Care was taken regarding the dosage such that it does not exceed 100 mg per day.

Research group: On the basis of the control group, 25 mg of agomelatine tablets (manufacturer: Jiangsu Hansoh Pharmaceutical Group Co., Ltd., Approved by the Chinese medicine, H20143375, specifications, 14 tablets×25 mg) was given orally before going to bed continuously for 6 w.

Research indicators:

Treatment efficiency: It was explained using different grades namely, markedly effective, effective and ineffective. It was considered to be markedly effective if all target lesions disappeared. If the sum of the long diameters of all target lesions decreased by >30 %, it was considered to be effective. Similarly if the sum of long diameters of all target lesions increased or decreased by <30 %, then it was said to be ineffective.

Total effective rate=marked rate+effective rate

Observation indicators:

Clinical effect: The clinical efficacy was evaluated using the HRSD score and the Pittsburgh Sleep Quality Index (PSQI) score. HRSD score reduction rate ≥75 % and PSQI score reduction rate ≥60 % are considered as cured; HRSD score reduction rate ≥50 % and PSQI score reduction rate ≥40 % are considered as markedly effective; HRSD score reduction rate ≥25 % and PSQI score reduction rate ≥20 % are considered to be valid and HRSD score reduction rate <25 % and PSQI score reduction rate <20 % are considered as invalid.

Total effective rate=cure rate+marked rate+effective rate

Positive and Negative Syndrome Scale (PANSS) scores: PANSS was used to evaluate the mental state of the patients, with a total of 30 characteristics, including positive, negative symptoms and general mental symptoms. Scores range of the scale had 1 to 7, in which higher scores indicated severity of the symptoms.

Depression score: Using the HRSD score depression score was studied. Full score in the scale was 52 points, and high score indicated more severe depressive symptoms.

Sleep quality index score: The PSQI includes characteristics such as sleep quality, sleep time, time to fall asleep, sleep efficiency, sleep disturbance, medication, and daytime dysfunction. The full score is 21 points and the higher score implied worst sleep quality.

Cognitive function: Cognitive function was studied using the Montreal Cognitive Assessment (MoCA) scale. The evaluation items included patients' memory, attention, executive function, language and spatial ability, etc. The total score is 30 points, and a score below 26 was considered to have cognitive impairment.

Adverse drug events: According to the study, the adverse drug events of the two drugs included digestive system adverse reactions, nervous system adverse reactions, reactive rash, sexual dysfunction, weight gain, and other adverse reactions. The incidence of adverse drug events in the two groups of patients during the medication was compared.

Statistical analysis:

The data involved in this study was analyzed using the Statistical Package of Social Sciences (SPSS) version 22.0 software, and passed the t or Chi-square (χ^2) test, and $p<0.05$ was considered statistically significant in the difference.

RESULTS AND DISCUSSION

Clinical curative effect was compared. After medication, the total effective rate of clinical curative effect in the research group was 95.56 %, which was 80 % higher than that in the control group ($p<0.05$) (Table 1).

Positive and negative symptom scores were evaluated. There was no significant difference in PANSS scores between the two groups before medication ($p>0.05$). After (3-6) w after medication, the PANSS scores of patients in the research group were significantly lower than those in the control group ($p<0.05$) (Table 2).

Depression score was compared which denoted no significant difference in HRSD scores between the two groups before medication ($p>0.05$). After 2 w, 4 w and 6 w of medication, the HRSD scores of the research group were lower than those of the control group ($p<0.05$) (Table 3).

Sleep quality index score was observed. Before medication, there was no significant difference in the PSQI scores of sleep quality characteristics between the two groups ($p>0.05$). After medication, the PSQI scores of sleep quality items in the research group were significantly lower than those in the control group ($p<0.05$) (Table 4).

Cognitive function score was compared between both the groups. Before medication, there was no significant difference in MoCA scores ($p>0.05$). After medication, MoCA scores in the research group were significantly higher than those in the control group ($p<0.05$) (Table 5).

Adverse drug reactions were also compared between both the groups. After medication, there were 7 patients with adverse drug events in the research group and 5 patients in the control group, and there was no significant difference between the two groups ($p>0.05$) (Table 6).

The results of this study showed that the clinical efficacy of sertraline alone was not as good as that of the combination of agomelatine. It shows that agomelatine and sertraline have played an interactive drug effect or agomelatine has played a better drug effect. Agomelatine and sertraline

share some pharmacological mechanisms in the treatment of depression. Both can inhibit the reuptake of serotonin by neurons, so that it can increase the concentration at nerve synapses. This same drug works by increasing serotonin activity levels to improve depressive symptoms. Both of them mediate the balance of the neurotransmitter system by increasing the content of serotonin in the patient's brain, because 5-HT is an important neurotransmitter, which is mainly involved in the regulation of mood, sleep and cognition. The drug achieves the effect of improving depressive symptoms by regulating the level of 5-HT. The research team combined the drug agomelatine, which has norepinephrine reuptake inhibitory effects in addition to serotonin reuptake thereby increasing the concentration of norepinephrine in the nerve synapses. This effect helps to increase the active levels of norepinephrine, improving depressive symptoms. Studies have shown that agomelatine has a certain curative effect on patients with mild to moderate depression, and can improve the symptoms of patients[5]. In this study, it is the interaction between drugs, or the drug effect of agomelatine, which needs further research. Studies have shown that agomelatine combined with sertraline in the treatment of depression can more effectively reduce anxiety symptoms, improve sleep quality, and have better and longer-lasting effects[6]. Studies have also confirmed that agomelatine and sertraline have different pharmacological mechanisms, and the combined application can exert synergistic effects in different aspects, thereby improving the therapeutic effect[7]. Judging from the research conclusions of others, the combination of agomelatine and sertraline can indeed improve the clinical efficacy, but it is still unknown whether the reason is agomelatine or the joint effect of the two drugs.

The PANSS score is used as a tool to assess schizophrenia and, in some patients, depression severity. Studies have found that patients with depression usually have lower PANSS scores[8]. A study showed that the reduction of PANSS score was related to the effect of drug treatment[9]. In this study, there was no significant difference in the PANSS scores of the two groups of patients before medication. However, PANSS scores of the research group were lower than the control group after medication, which indicated that the drug treatment effect of the study group was better than that of the control group. HRSD score is directly related to drug treatment

TABLE 1: COMPARISON OF CLINICAL EFFECTS OF THE TWO GROUPS OF DRUGS (x̄±s)

Group	n	Cure	Markedly effective	Valid	Invalid	Total effective rate
Research	45	3	28	12	2	95.56 %
Control	45	1	22	13	9	80 %
χ^2						5.258
p						0.001

TABLE 2: COMPARISON OF PANSS SCORES BETWEEN THE TWO GROUPS (x̄±s)

Group	n	PANSS score		
		Before medication	Medication for 3 w	Medication for 6 w
Research	45	58.62±4.36	40.58±4.26	30.62±3.16
Control	45	58.39±4.28	45.82±4.47	38.45±3.35
t		0.014	1.385	1.826
p		0.928	0.001	0.000

TABLE 3: COMPARISON OF HRSD SCORES BETWEEN THE TWO GROUPS (x̄±s)

Group	n	Before medication	Medication for 2 w	Medication for 4 w	Medication for 6 w
Research	45	23.14±1.54	18.32±1.38	13.52±1.28	9.06±1.02
Control	45	23.08±1.46	20.42±1.41	16.24±1.31	12.55±1.18
t		0.024	1.135	1.206	1.258
p		0.901	0.002	0.001	0.001

TABLE 4: COMPARISON OF PSQI SCORES BEFORE AND AFTER TREATMENT IN THE TWO GROUPS (x̄±s)

Sleep quality index components	Research group		Control group	
	Before medication	After medication	Before medication	After medication
Sleep quality	2.36±0.28	1.22±0.19[b1]	2.35±0.28	1.91±0.27[b]
Bedtime	2.42±0.28	1.36±0.18[b1]	2.43±0.29	1.88±0.26[b]
Sleeping time	2.26±0.25	1.32±0.17[b1]	2.27±0.25	1.82±0.24[b]
Sleep efficiency	2.31±0.27	1.23±0.15[b1]	2.3±0.27	1.91±0.31[b]
Sleep disturbance	2.44±0.29	1.41±0.19[b1]	2.42±0.28	1.92±0.31[b]
Hypnotic drugs	2.51±0.29	1.01±0.09[b1]	2.49±0.28	1.58±0.19[b]
Day function	2.54±0.29	1.18±0.13[b1]	2.53±0.29	1.86±0.24[b]
PSQI total score	16.83±0.28	8.73±0.16[b1]	16.79±0.28	12.88±0.26[b]

Note: [b]p<0.05 and [1]p<0.05 compared with the control group before treatment

TABLE 5: COMPARISON OF MoCA SCORES BETWEEN THE TWO GROUPS OF PATIENTS (x̄±s)

Group	n	Before medication	After medication
Research	45	22.18±1.32	26.02±1.36
Control	45	22.14±1.41	24.12±1.28
t		0.032	0.756
p		1.012	0.001

TABLE 6: COMPARISON OF ADVERSE DRUG EVENTS BETWEEN THE TWO GROUPS (x̄±s)

Group	n	Digestive system adverse reactions	Nervous system adverse reactions	Reactive rash	Sexual dysfunction	Weight gain	Other	Total incidence
Research	45	2	3	1	0	1	0	15.56 %
Control	45	1	2	2	0	0	0	11.11 %
χ^2								0.187
p								0.716

effect. The therapeutic goals of sertraline and agomelatine are to relieve depressive symptoms and improve the psychological status of the patients. Higher HRSD scores tend to indicate more severe depressive symptoms, while lower HRSD scores indicate reduction of depressive symptoms. As a clinical assessment tool, HRSD score sometimes cannot completely reflect the patient's symptoms and curative effect. It is often found that the patient's sleep quality and appetite improve but the HRSD score does not changed significantly. Studies have found that there is a positive correlation between HRSD score and drug efficacy[10]. However, studies also explain that this correlation is not strong. Sometimes drug treatment does not improve the depressive symptoms of patients, but the HRSD score has changed significantly[11]. Sertraline and agomelatine, as commonly used antidepressants, have a certain effect on improving sleep quality. Studies have pointed out that sertraline can improve the sleep quality of depressed patients[12]. It can reduce patients' difficulty in falling asleep, improve sleep effect and prolong sleep time, and has a certain effect in reducing the wake up time at night. Sertraline reduces the rate of Rapid Eye Movement (REM) sleep. For this effect, it may be associated with the effect of sertraline on serotonin receptors and histamine receptors. As a dual-action antidepressant, agomelatine acts not only on the dopamine system but also on the histamine system. Agomelatine can inhibit the reuptake of dopamine, which can improve the attention and alertness of patients, thereby improving the quality of sleep of patients. Agomelatine can also antagonize the Histamine (H1) receptor, which can reduce the patient's drowsiness and the number of wake-ups during sleep, thereby improving the quality of sleep. This explains that the PSQI score of the patients in the study group was lower than that in the control group.

Sertraline and agomelatine are two common antidepressants, which may have different pharmacological mechanisms in improving the

MoCA score of depressed patients. Sertraline works by increasing the activity of serotonin, which may help improve cognitive function in depressed patients, including memory, attention and executive function. As a selective serotonin and melatonin receptor agonist, agomelatine improves the depressive symptoms of patients by simultaneously increasing the activity of serotonin and simulating the effect of melatonin. As an important biological clock regulator, melatonin is involved in the process of regulating the sleep-wake cycle. Agomelatine may indirectly improve the cognitive function of depressed patients by regulating the biological clock and sleep quality. Studies have found that sertraline can improve the cognitive function of patients with depression, which may be related to the regulation of sertraline on 5-HT in the brain[13]. The adverse drug reactions of sertraline and agomelatine mainly include dizziness, headache, nausea, diarrhea, and rashes. Overall, the adverse drug reactions of the two drugs were within an acceptable range. A study found that about 10 %-20 % of sertraline users had adverse reactions such as nausea, diarrhea, and stomach pain[14]. In this study, adverse drug reactions in the research group were slightly higher than those in the control group, which may be related to the interaction of the two drugs.

To sum up, the simple use of sertraline has a certain effect on patients from mild to moderate depression, but the combination with agomelatine has better clinical effects and can help relieve patients' depressive symptoms, improve their sleep quality, cognitive function and has high drug safety.

Conflict of interests:

The authors declared no conflict of interest.

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